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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 10/826,919      | 04/16/2004  | Alexander Deiters    | 54-000250US         | 1323             |

22798            7590            03/27/2008  
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|----------------------|
| EXAMINER             |
| GEBREYESUS, KAGNEW H |

|          |              |
|----------|--------------|
| ART UNIT | PAPER NUMBER |
| 1656     |              |

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|------------|---------------|
| MAIL DATE  | DELIVERY MODE |
| 03/27/2008 | PAPER         |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

|                              |                        |                     |  |
|------------------------------|------------------------|---------------------|--|
| <b>Office Action Summary</b> | <b>Application No.</b> | <b>Applicant(s)</b> |  |
|                              | 10/826,919             | DEITERS ET AL.      |  |
|                              | <b>Examiner</b>        | <b>Art Unit</b>     |  |
|                              | KAGNEW H. GEBREYESUS   | 1656                |  |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 04 February 2008.
- 2a) This action is FINAL.                    2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1-61 is/are pending in the application.
  - 4a) Of the above claim(s) 1-51, 60 and 61 is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 52-59 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.
 

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  - a) All    b) Some \* c) None of:
    1. Certified copies of the priority documents have been received.
    2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
    3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

|  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____ .                                    |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>11/8/04, 11/19/07</u> .                                       | 6) <input type="checkbox"/> Other: _____ .                        |

**DETAILED ACTION**

Applicant's election without traverse dated February 04, 2008 in response to the supplemental restriction requirement mailed on January 02, 2008 is acknowledged. Applicants have elected Group XIV (claims 52-59) with further election of the species: "a derivative of polyethylene glycol" and the orthogonal tRNA synthetase of SEQ ID NO: 48. Claims 1-51, 60-61 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to non-elected groups, there being no allowable or linking claims. Additional species will be examined upon allowance of the first species. The inventions of Group II and III are drawn to products that can be used in an unrelated processes. The elected group XIV is drawn to a method of producing a protein comprising unnatural amino acids wherein said unnatural amino acid can further be modified.

**Therefore this requirement is made final.**

***Priority***

Priority for this application is acknowledged for benefit of U.S. Provisional Application 60/479931, filed on June 18, 2003, and U.S. Provisional Application 60/493014 filed on August 05, 2003 and U.S. Provisional Application No. 60/496548, filed on August 19, 2003. Claim 53-59 (generic claim) in the instant application are not supported by provisional application 60/493014 and 60/479931. However these claims are supported by Provisional Application No. 60/496,548 filed on August 19, 2003.

***Information Disclosure Statement***

The information disclosure statement filed on November 8, 2004 and November 19, 2007 for which a copy of the patent publication has been submitted in this application has been considered as shown by the Examiners signature next to each reference.

***Oath/Declaration***

The oath or declaration submitted on July 26, 2004 has been reviewed and is in compliance with 37 CFR 1.56.

***Specification***

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code in paragraphs [0185] and [0295]. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See M.P.E.P. § 707.05(e) for the acceptable notation of an Internet address.

Furthermore the specification is objected to for an unclear incorporation by reference. In paragraphs [0178] and [0182], reference to a related case by attorney docket number is unclear. The Examiner suggests use of either the Patent Application Publication number of the other application (preferable) or the application number for clarity. Correction is required.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 53-56, 58 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schultz et al US 6,927,042 (priority claimed Jan. 16, 2003 **in IDS**) in view of Wang et al (Bioconjugation by Copper(I)-Catalyzed Azide-Alkyne [3+2] Cycloaddition **in IDS**) further in view of Chin et al (Addition of *p*-azido-L-phenylalanine to the genetic code of *Escherichia coli*, J. Am. Chem. Soc. 2002, vol. 124, 9026-9027, published on the Web on 07/11/2002 **in IDS**).

Schultz et al teach an in-vivo method comprising using orthogonal tRNA synthetase/orthogonal tRNA pairs (ORS/OtRNA pairs) to incorporate an unnatural amino acid comprising a 1<sup>st</sup> reactive group (electrophilic or a nucleophilic) into a protein in a cell followed by reacting said cell comprising the modified protein with a compound comprising a 2<sup>nd</sup> reactive group (nucleophilic or electrophilic) such as a saccharide (carbohydrate) moiety.

Furthermore Schultz et al teach that the unnatural amino acid comprising a 1<sup>st</sup> reactive group can be a keto or an aldehyde group and the compound

Art Unit: 1656

comprising a 2<sup>nd</sup> reactive group can have any of a variety of nucleophilic azides such as hydrazide, semicarbazide or hydroxylamines or alkyls having 1-6 carbons (see claim 4, 5). Schultz et al. do not specifically teach that the 2<sup>nd</sup> reactive group is attached to the 1<sup>st</sup> reactive group through a [3+2] cycloaddition reaction.

Wang et al teach that azides and alkynes can be easily introduced into biological molecules by organic synthesis, chemical conjugation or via biosynthetic pathways. such as a process that uses ORS/OtRNA pairs as described by Chin et al. (see Wang et al., page 3192, 1<sup>st</sup> paragraph column 1).

Wang et al teach attaching azides or alkynes to the exterior surface of the coat protein of cow mosaic virus (CPMV) at reactive lysine or cysteine residues wherein viruses thus modified are reacted with fluorescein derivatives (dyes) (which contains a complementary alkyne or azide group) thus resulting in coupling of the azide (or alkyne) group with the alkyne (or azide) group of a fluorescien dye through a [3+2] cycloaddition reaction.

Although Wang et al clearly indicate that a biosynthetic pathway using ORS/OtRNA can be used their method was performed in-vitro. However Wang et al suggest that azides and alkynes can be introduced into proteins via biosynthetic pathways and refer to a process that uses ORS/OtRNA pairs described in Chin et al. (see Wang et al., page 3192, 1<sup>st</sup> paragraph column 1).

Therefore, it would have been obvious for a person of ordinary skill in the art to combine Schultz et al's in vivo cell based method with the method of Wang

et al to attach an unnatural amino acid comprising either an alkyne or azido moiety to a fluorescein conjugate to a protein.

One of skill in the art would have reasonable expectation of success because the state of the art at the filing of the instant application was such that methods of using ORS/OtRNA pairs for incorporating unnatural amino acids were well known. Furthermore attaching novel functional groups such as fluorescent compounds were known in the art. For example Cornish et al. (Site-specific Protein Modification Using Ketone handles. J. Am. Chem. Soc. Vol. 118, No 34, 1996) teach attaching a commercially available fluorescein hydrazide to an unnatural keto amino acid in a T4 lysozyme protein.

One of ordinary skill in the art would be motivated to combine the above teachings in view of producing proteins comprising novel functionalities, to produce glycoproteins or to attach compounds such as polyethylene glycol that stabilize and/or to moderate antigenicity of therapeutic proteins in the circulation.

### ***Double Patenting***

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Art Unit: 1656

Claims 52-59 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 52-59 of copending Application No. 10/561,121. (PG US2006/0246509 A1). This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claim 52 is provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 123 of copending Application No. 10/825,867 (PG US/2005/0009049 A1).

This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

**Conclusion:**

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KAGNEW H. GEBREYESUS whose telephone number is (571)272-2937. The examiner can normally be reached on 8:30am-5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kagnew H Gebreyesus PhD/  
Examiner, Art Unit 1656  
3/7/2008

/Robert B Mondesi/  
Primary Examiner, Art Unit 1652